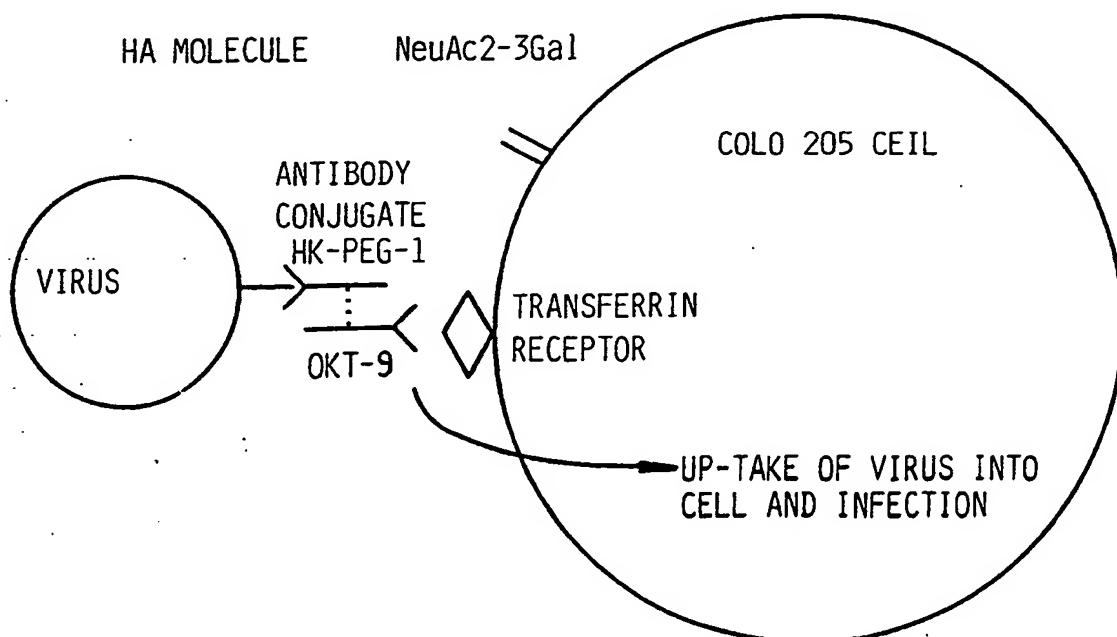




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<p>(21) International Application Number: PCT/SE92/00745</p> <p>(22) International Filing Date: 28 October 1992 (28.10.92)</p> <p>(30) Priority data: 9103183-1 30 October 1991 (30.10.91) SE</p> <p>(71) Applicant (for all designated States except US): THERA GENE HB [SE/SE]; Östra Björnvägen 8, S-430 411 Kullavik (SE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): LINDHOLM, Leif [SE/SE]; Östra Björnvägen 8, S-430 41 Kullavik (SE). ENERBÄCK, Sven [SE/SE]; Slätthultsliden 13A, S-431 69 Mölndal (SE). STRANNEGÅRD, Örjan [SE/SE]; Lekevallsgatan 6, S-431 69 Mölndal (SE).</p>	<p>(74) Agent: AWAPATENT AB; Box 45086, S-104 30 Stockholm (SE).</p> <p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).</p> <p>Published <i>With international search report.</i></p>	

(54) Title: TARGETED DELIVERY OF VIRUS VECTOR TO MAMMALIAN CELLS



(57) Abstract

A complex between a virus the cell binding receptor of which has been inactivated and an antibody, said antibody having the ability to interact with a specific antigen on the surface of a mammalian cell different from the cellular structure which would otherwise mediate binding of the virus to the cell surface and which antigen has the ability to mediate entrance of a virus vector or infectious virus into mammalian cells.

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TARGERED DELIVERY OF VIRUS VECTOR TO MAMMALIAN CELLS

The present invention relates to a complex between a virus the cell binding receptor of which has been inactivated and an antibody. The invention is applicable to situations where it is desireable to introduce viruses into selected mammalian cells for medicinal purposes.

Viruses enter mammalian cells following binding between a viral receptor and a chemical structure, or ligand, in the cell membrane. This initial binding is a first and necessary step leading to the entry of virus into the cell and the subsequent transcription of the viral genome and replication of the virus within the cell. Rather detailed knowledge about the structure and specificity of many viral receptors is at hand. For example, in the case of influenza virus the specificity of the virus receptor is analogous to the specificity of antibodies against certain tumor antigens, in that the influenza virus hemagglutinin binds to NeuAc2-3Gal-R, which is present on the same structures as many human tumor associated antigens.

The main object of the present invention is to provide techniques enabling introduction of viruses into mammalian cells for providing desired biological action in such cells.

Another object of the invention is to enable virus vectors or infectious viruses to be directed to specific cells in a living animal body.

Yet another purpose is to provide techniques making it possible for viruses to selectively enter specific cells in a living animal body.

For these and other purposes the invention provides for a complex between a virus and an antigen-binding substance selected from antibodies, fragments of antibodies and antigen-binding peptides, the cell binding receptor of said virus being inactivated. Said substance

has the ability to interact with a specific antigen on the surface of a mammalian cell which antigen is different from the cellular structure which would otherwise mediate binding of the virus to the cell surface. Furthermore, said substance has the ability to mediate entrance of a virus vector or infectious virus into the cell.

The substance can either be a monoclonal antibody or a fragment of a whole antibody.

The substance can be bound to the virus in different ways, such as by chemical conjugation; by bridging the substance to the virus by an immunochemical reagent, or by using a bifunctional substance binding to the virus as well as to a cellular antigen.

The substance may also be expressed on the virus surface envelope following cloning into the virus genome of gene(s) for whole antibodies or fragments thereof.

The inactivation of the viral cell receptor in accordance with the present invention can take place by chemical means, by a specific antibody or by gene technological manipulation of the viral genome. Thus, the gene for the viral cell receptor or parts thereof can be replaced with antibody genes.

The complex according to the present invention is intended for medicinal use. Thus, the complex can be used as a vector to introduce genes into cells or organs for specific therapeutical purposes. The complex may also be used to express viral antigens on the cell surface for such purposes or it can be used to cause an infection in cells carrying the substance against which the antibody is reactive.

By using an antibody which binds to a cellular membrane antigen which can be internalized into the cell, virus can bind to the cell via an antibody-antigen reaction and then penetrate into the cell and replicate causing a viral infection. Furthermore, since antigens are known which are more or less unique for certain types of cells, virus can be selectively directed to enter and in-

fect specific cells in the body. Examples of such antigens are some cell-differentiation antigens, such as CD19 on B cells, and certain tumor-associated antigens on carcinoma cells.

The invention will therefore make it possible to direct virus vectors or infectious viruses to specific cells in the body with the possibility of introducing functional genes into selected cells or organs in vivo or to cause a viral infection in certain cells.

The following table shows examples of viral receptors and their cellular ligands. Receptors such as these are possible candidates for use within the present invention.

TABLE 1

Some viral receptors and their cellular ligands.

<u>Virus</u>	<u>Cellular ligand</u>	<u>Distribution</u>	<u>Viral receptor</u>
Epstein-Barr	CD21	B cells	gp350/220
Influenza A	Sialyloglycolipid or Sialyloglycoprotein containing NeuAc2-3Gal-R	Many cell types	Hemagglutinin
Paramyxovirus prot	Sialic acid-containing carbohydrates	Many cell types	HN, H and G
Retrovirus Protein		Many cell types	SU protein

When virus replicates in the cell certain viral proteins are degraded to peptides. These peptides are bound to so called MHC antigens within the cell and are thereafter transported to the cell membrane where the peptide-MHC complex serve as target for a very important defense system, i.e. virus specific cytotoxic T cells, which actu-

ally kill the virus infected cell. Certain virus, e.g. retroviruses, are integrated into the host cell genome in the form of provirus which may thereafter be replicated. By "genetic engineering" methods retroviruses can be manipulated so that they no longer replicate but can be used as vectors to introduce new genes into mammalian cells. The use of retroviral vectors offers a practical means for gene therapy in humans. However, at the present time the use of retroviral vectors are largely restricted to cells of hemopoietic origin.

There are several technical routes along which the cell-binding receptor of a virus can be replaced with an antibody. Some principal ways are listed below and illustrated in the appended drawings, viz. figures 1 to 3.

1. The viral receptor can be blocked with an antibody which may in turn be conjugated with an antibody of the desired specificity.

2. The viral receptor can be inactivated by chemical- or gene technological methods and the replacing antibody can then be chemically coupled directly to the virus particle.

3. The gene for the viral receptor can be replaced with the genes for the replacing antibody.

The possibilities inherent in this invention are many. One area is gene therapy in humans where retroviral vectors have already been used to introduce genes into human cells for therapeutical purposes. The present invention may be expected to increase the efficiency of this approach as well as making possible new areas of use, such as the deliberate introduction of genes into tumor cells.

Another area is immunotherapy of tumor diseases where the invention might be used for gene therapy or to introduce virus into tumor cells with the intent of expressing viral antigens at the cell surface converting the cells into possible targets for the virus-specific cytotoxic T cells.

The invention will be further illustrated in the following by specific examples which are not construed to restrict the scope of the invention otherwise than defined by the appended claims.

EXAMPLE 1

The following examples demonstrate that the binding specificity of a virus can be blocked and replaced with that of an antibody. In the examples the binding and infection of Influenza virus A/PR/8 to human colon carcinoma cells Colo 205 is used. The cell binding of influenza virus is depending on a specific binding molecule, Hemagglutinin (HA), which is present in the viral envelope, and which binds to NeuAc2-3Gal-R, present on many mammalian cells.

In this example the following strategy was employed.

1. The binding of A/PR/8 to the target cell was blocked by means of the monoclonal antibody HK-PEG-1 against influenza HA (Koprowski H, Gerhard W and Croce CM: Production of antibodies against influenza virus by somatic cell hybrids between mouse myeloma and primed spleen cells. Proc.Natl.Acad.Sci USA, Vol. 74, pp 2985-2988, 1977). The cell line producing this antibody is obtainable from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, USA.

2. A new binding specificity was conferred on the virus by another antibody which had been chemically conjugated to the HK-PEG-1 antibody used to block the natural cell binding of the virus. The antibody OKT9 (US Patent 4,364,934) which reacts with the transferrin receptor on proliferating mammalian cells was used for this purpose. An antibody against the transferrin receptor was used because the transferrin receptor is rapidly and constitutively internalized by the cells along with an antibody which has been reacted with the receptor (Schwartz AL: Cell Biology of Intracellular Protein Trafficking, Ann.Rev.Immunol., Vol 8, pp 195-229, 1990). The cell line

producing the OKT9 antibody is obtainable from the American Type Culture Collection.

The expected dual effect on virus binding of the antibody conjugate used is schematically shown in Fig. 4 of the drawings.

EXAMPLE 2

Influenza A/PR/8 was obtained from Statens Bakteriologiska Laboratorium, S-10521 Stockholm, Sweden.

HK-PEG-1 and OKT9 antibody

Hybridoma cells were obtained from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, USA. Hybridoma cells were grown in Iscove's medium supplemented with 10% fetal calf serum. Antibody production was performed in dialysis tubings (Sjögren-Jansson E and Jeansson S: Large-Scale Production of Monoclonal Antibodies in Dialysis Tubing, J.Immunol.Meth., Vol 84, pp 359-364, 1985) and antibodies were purified by affinity chromatography on a Protein A Sepharose CL-4B (Pharmacia, Uppsala, Sweden)(Ey PL, Prowse SJ and Jenkin CR: Isolation of pure IgG₁, IgG_{2a} and IgG_{2b} immunoglobulins from mouse serum using Protein A-Sepharose. Immunology Vol 15, pp 429-436, 1978).

Antibody conjugates:

Antibody conjugates were prepared using the heterobifunctional reagent N-succinimidyl (2 pyridyldithio)propionate, SPDP (Pharmacia, Uppsala, Sweden) (Carlsson J, Drevin H and Axén R: Protein thiolation and reversible protein protein conjugation. N-succinimidyl 3(2 pyridyldithio)propionate - a new heterobifunctional reagent. Biochem.J., Vol 173, pp 723-737, 1978). Conjugates were purified from unreacted antibody by gel filtration on Superdex 200 (Pharmacia, Uppsala, Sweden).

Titration of virus by Hemagglutination:

Hemagglutination of human blood group O red blood cells was performed in 96-well trays using standard methods (Mahy BWJ, ed: Virology, a practical approach. IRL Press, Oxford, 1985).

Colo 205 colon carcinoma cells were obtained from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, USA, and maintained in Iscove's medium with 10% fetal calf serum.

ResultsInhibition of viral binding by HK-PEG-1 antibody and HK-PEG-1 conjugates.

Inhibition of viral binding to its cellular ligand was measured by the hemagglutination method. Virus, 800 HAU (HemAgglutinating Units)/ml, was incubated for 1h at room temperature with antibody at different concentrations and then allowed to agglutinate human red blood cells. HK-PEG-1 antibody caused complete inhibition of agglutination at 7µg/ml or more whereas the corresponding figure for HK-PEG-1 conjugated to OKT9 was 10 µg/ml.

Ability of HK-PEG-1 conjugates to mediate viral infection.

HK-PEG-1 or HK-PEG-1 conjugated to OKT9 was incubated with 100 HAU of A/PR/8 virus for 1 hour at room temperature in order to block the HA molecules in the viral envelope. Thereafter the virus preparations were incubated together with 2×10^6 Colo 205 cells in 1 ml PBS for 1 hour at 37°. The cells were washed three times with PBS by centrifugation, suspended in 1 ml of complete medium and incubated at 37° for 24 hours. Presence of virus in the medium was assessed by hemagglutination. The results are shown in Table 2 below. It is evident that the conjugation of OKT9 to HK-PEG-1 allows the virus to infect the cells by giving the virus a new binding site in the cell membrane, thereby overcoming the inhibition caused by the HK-

PEG-1 antibody alone. The decreasing infectivity with increasing antibody concentration is probably an effect of formation of large virus-antibody complexes since such complexes are less effectively taken up into the cell.

TABLE 2

Production of virus as measured by hemagglutination by Colo 205 cells infected with Influenza A/PR/8 pretreated with different antibodies.

<u>Antibody</u>	<u>Concentration (µg/ml</u>	<u>HA-titer</u>
None		1/16
HK-PEG-1	30	Negative (<1/2)
HK-PEG-1	100	Negative (<1/2)
HK-PEG-1	300	Negative (<1/2)
HK-PEG-1/OKT9	30	1/8
HK-PEG-1/OKT9	100	1/4
HK-PEG-1/OKT9	300	1/2

CLAIMS

1. A complex between a virus the cell binding receptor of which has been inactivated and an antigen-binding substance selected from antibodies, fragments of antibodies and antigen-binding peptides, said substance having the ability to interact with a specific antigen on the surface of a mammalian cell different from the cellular structure which would otherwise mediate binding of the virus to the cell surface and which antigen has the ability to mediate entrance of a virus vector or infectious virus into mammalia. cells.

2. The complex according to claim 1, wherein the substance is a monoclonal antibody.

3. The complex according to claim 1, wherein the substance is a fragment of a whole antibody, whether prepared by chemical means or by expression of antibody genes or DNA sequences containing information derived from antibody genes.

4. The complex according to claim 1, wherein the substance is an antigen-binding peptide, whether derived from an antibody sequence or not.

5. The complex according to any preceding claim, wherein the substance is bound to the virus by chemical conjugation.

6. The complex according to any preceding claim, wherein the substance is bridged to the virus by an immunochemical reagent, such as an anti-species antibody, avidin or streptavidin.

7. The complex according to any preceding claim, wherein the substance is a bifunctional antibody binding to a virus as well as to a cellular antigen.

8. The complex according to any of claims 1 to 4, wherein antibody binding site(s) is (are) expressed on the viral surface following cloning of antibody gene(s) or DNA

sequence(s) coding for antibody binding structure(s) into the viral genome.

9. The complex according to any of claims 1 to 4, wherein the substance is reactive with a cellular antigen capable of mediating entry of a virus into a cell.

10. The complex according to any preceding claim, wherein the viral cell receptor has been inactivated by chemical means, by a specific antibody or by gene technological manipulation of the viral genome.

11. The complex according to any of claims 1 to 9, wherein the gene for the viral cell receptor or parts thereof has been replaced with antibody genes.

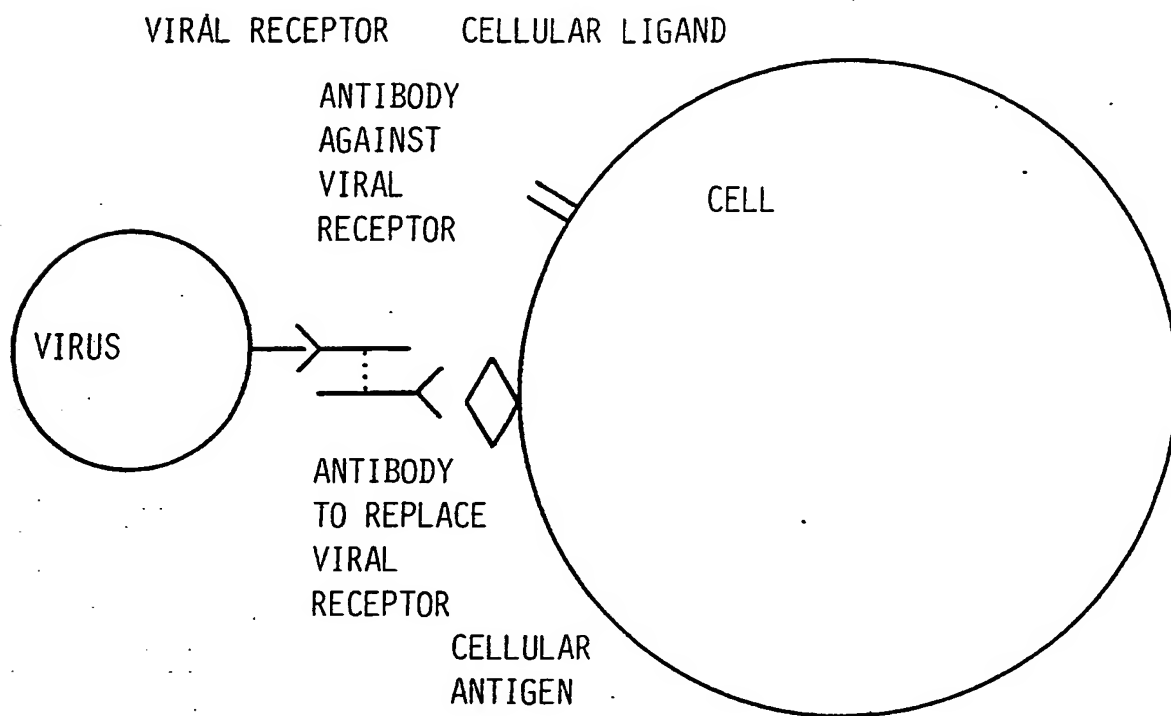
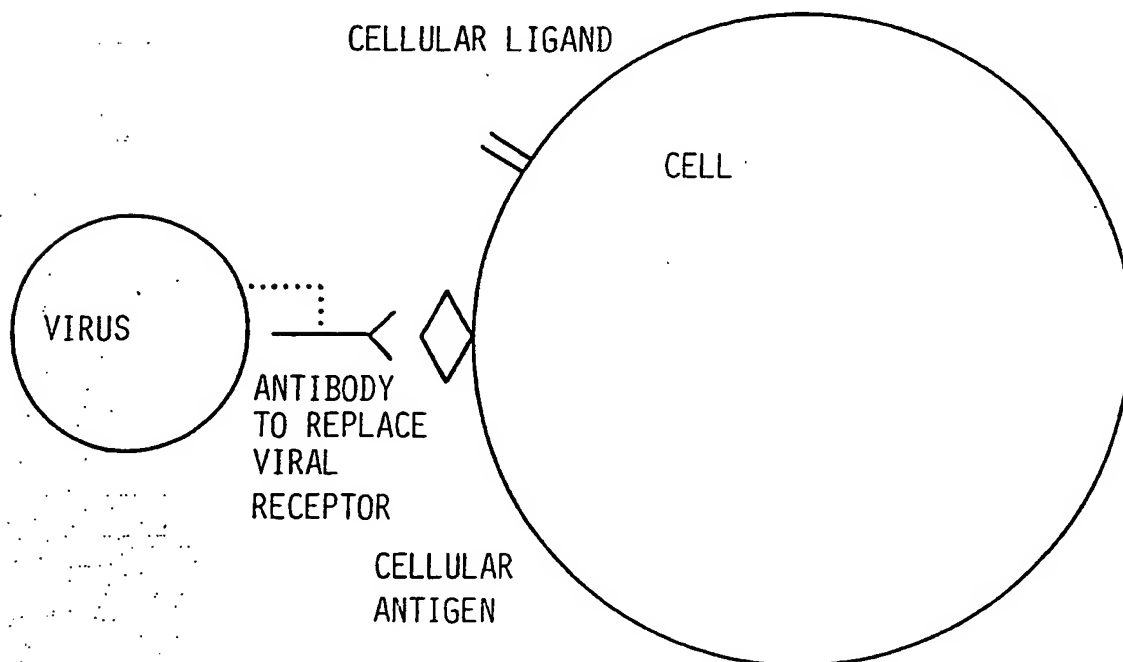
12. The complex according to any preceding claim for medicinal use.

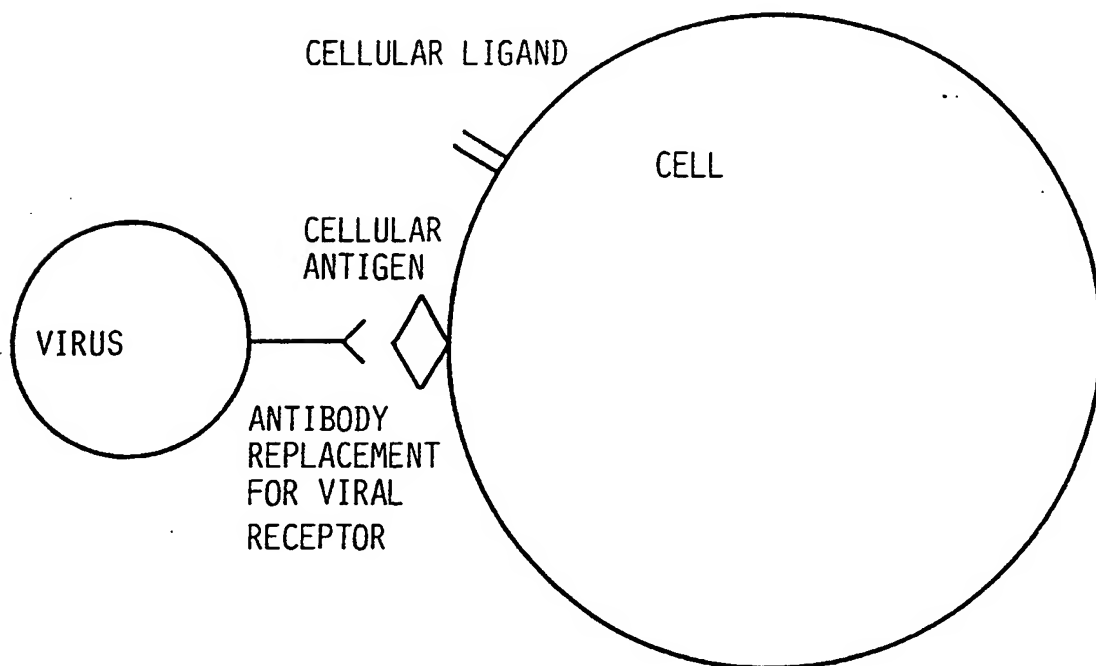
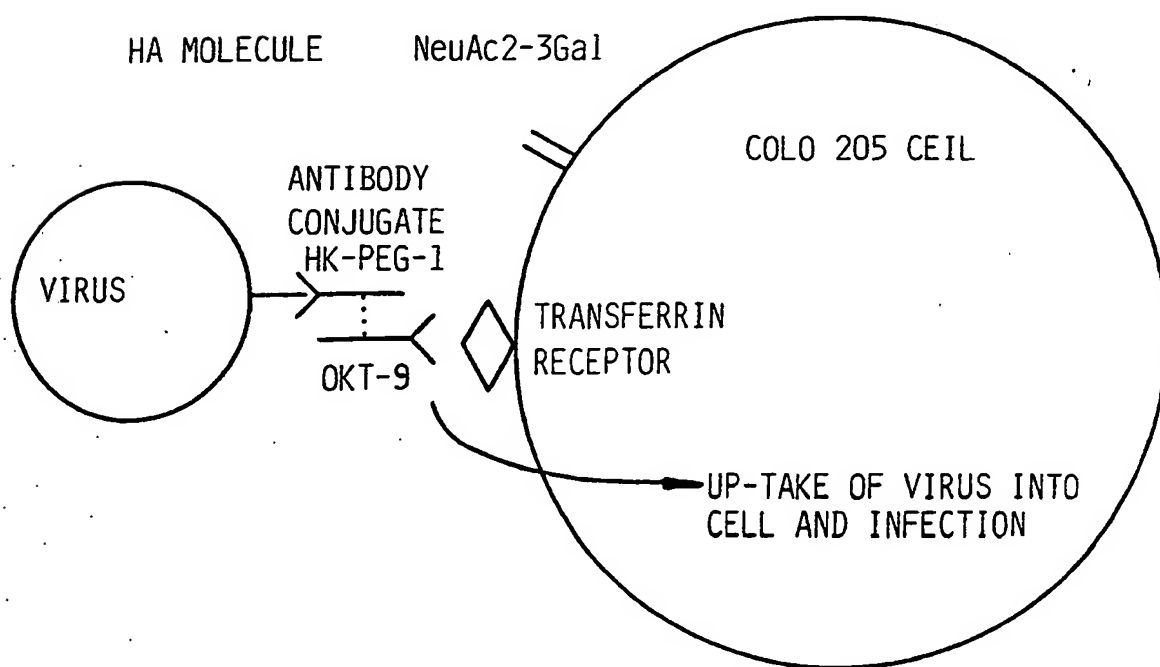
13. The complex according to claim 12 for use as a vector to introduce genes into cells or organs for therapeutic purposes.

14. The complex according to claim 13 for use to express viral antigens on the cell surface for therapeutic purposes.

15. The complex according to claim 13 for use for therapeutic purposes to cause an infection in cells carrying the antigen against which the substance is reactive.

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FIG.1**1.REPLACING ANTIBODY CONJUGATED TO BLOCKING ANTIBODY****FIG.2****2.REPLACING ANTIBODY CONJUGATED TO VIRUS**

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FIG.3**3.VIRAL GENE FOR RECEPTOR REPLACED WITH ANTIBODY GENES****FIG.4**

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 92/00745

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 12 N 5/10, 15/87, A 61K 48/00, 39/00														
II. FIELDS SEARCHED <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; border: 1px solid black; padding: 5px;">Classification System</td> <td style="border: 1px solid black; padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; height: 40px; vertical-align: bottom;">IPC5</td> <td style="border: 1px solid black; padding: 5px; height: 40px; vertical-align: bottom;">C 12 N</td> </tr> </table> <div style="text-align: center; margin-top: 10px; font-size: small;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div> <p style="margin-top: 20px;">SE,DK,FI,NO classes as above</p>			Classification System	Classification Symbols	IPC5	C 12 N								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category¹⁰</th> <th style="width: 70%; padding: 5px;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">FR, A, 2649119 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE) 4 January 1991, see page 3, line 1 - line 2; page 3, line 16 - page 5 claims --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-15</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">Proc. Natl. Acad. Sci., Vol. 86, December 1989 Pierre Roux et al.: "A versatile and potentially general approach to the targeting of specific cell types by retroviruses: Application to the infection of human cells by means of major histocompatibility complex class I and class II antigens by mouse ecotropic..", see page 9079 - page 9083 --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-15</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">WO, A1, 9012087 (NOVACELL CORPORATION) 18 October 1990, see page 18, line 21 - page 20, line 20; page 22, line 22 - line 37; claims 10-18 --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-15</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	FR, A, 2649119 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE) 4 January 1991, see page 3, line 1 - line 2; page 3, line 16 - page 5 claims --	1-15	X	Proc. Natl. Acad. Sci., Vol. 86, December 1989 Pierre Roux et al.: "A versatile and potentially general approach to the targeting of specific cell types by retroviruses: Application to the infection of human cells by means of major histocompatibility complex class I and class II antigens by mouse ecotropic..", see page 9079 - page 9083 --	1-15	X	WO, A1, 9012087 (NOVACELL CORPORATION) 18 October 1990, see page 18, line 21 - page 20, line 20; page 22, line 22 - line 37; claims 10-18 --	1-15
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 60%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 35%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border: 1px solid black; padding: 5px;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; text-align: center;">8th February 1993</td> <td style="border: 1px solid black; padding: 5px; text-align: center;">09 -02- 1993</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">International Searching Authority</td> <td style="border: 1px solid black; padding: 5px;">Signature of Authorized Officer</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px; text-align: center;">SWEDISH PATENT OFFICE</td> <td style="border: 1px solid black; padding: 5px; text-align: center;">Carl Olof Gustafsson</td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	8th February 1993	09 -02- 1993	International Searching Authority	Signature of Authorized Officer	SWEDISH PATENT OFFICE	Carl Olof Gustafsson				
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	WO, A3, 9102805 (VIAGENE, INC.) 7 March 1991, see page 14, line 24 - line 26; page 14, line 28 - line 37; page 84, line 26 - page 86, line 14; page 90 --	1-15
A	WO, A2, 8907136 (WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH) 10 August 1989, see page 17, line 13 - page 20, line 14 --	1-15
A	WO, A1, 9104753 (CETUS CORPORATION) 18 April 1991, see page 3, line 32 - page 4; page 9 - page 12; page 24, line 10 - line 12; claims 13-14 --	1
A	Proc. Natl. Acad. Sci., Vol. 87, April 1990 Jean-Paul Leonetti et al.: "Antibody-targeted liposomes containing oligodeoxyribonucleotides complementary to viral RNA selectively inhibit viral replication", see page 2448 - page 2451 --	1
P,X	WO, A, 9206180 (UNIVERSITY OF CONNECTICUT) 16 April 1992, see page 5, line 5 - line 6 claims -- -----	1

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 92/00745**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 08/01/93
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2649119	91-01-04	NONE	
WO-A1- 9012087	90-10-18	EP-A- 0466815 JP-T- 4504361	92-01-22 92-08-06
WO-A3- 9102805	91-03-07	AU-D- 6185390 EP-A- 0487587	91-04-03 92-06-03
WO-A2- 8907136	89-08-10	EP-A- 0400047 JP-T- 3503718	90-12-05 91-08-22
WO-A1- 9104753	91-04-18	NONE	
WO-A- 9206180	92-04-16	AU-D- 8860391	92-04-28